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(54) Title: PROCESS FOR THE PRODUCTION OF ATORVASTATIN CALCIUM IN AMORPHOUS FORM

(57) Abstract: A process for the preparation of atorvastatin calcium in amorphous form is disclosed. The process comprises (i) treating diol protected tert-butyl ester with a methanolic solution in the presence of an aqueous acid; (ii) adding aqueous hydroxide solution to the reaction mixture; and removing unreacted diol protected tert-butyl ester (a) by solvent extraction (iii) treating the product obtained in step (ii) with calcium chloride solution to obtain crude amorphous atorvastatin calcium salt; (iv) isolating said crude salt; (v) treating crude product so isolated with activated carbon in aqueous ethyl acetate (vi) recovering the product by addition of non polar hydrocarbon solvent filtration and drying to produce pure amorphous atorvastatin calcium.

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PROCESS FOR THE PRODUCTION OF ATORVASTATIN CALCIUM IN AMORPHOUS FORM

FIELD OF THE INVENTION

5

The present invention relates to a novel process for the production of atorvastatin calcium. Particularly, the present invention relates to a novel process for the production of amorphous atorvastatin calcium. More particularly, the present invention relates to a novel process for the production of amorphous atorvastatin calcium from a diol protected tert-butyl ester (a).

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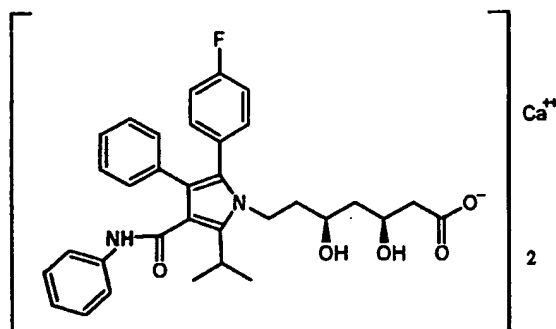
BACKGROUND OF THE INVENTION

[R-(R*,R*)]-2-(4-FLUOROPHENYL)- β,δ -DIHYDROXY-5-(1-METHYLETHYL) PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID, commonly known as atorvastatin is known to be therapeutically useful compound. Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. Open dihydroxy carboxylic acid, lactone and various salt forms of atorvastatin have been synthesized.

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According to the disclosure contained in the United States Patent 5,273,995, describes that R-form of the ring opened acid form has surprising inhibition of the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula 1:

25



is more suited to formulations and has been recommended as a drug.

United states patents 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,273,995; 5,280,126; 5,298,627; 5,342,952; 5,385,929; 5,397,792; 5 European Patent 409,281; and PCT publication No. 8,907,598 describe various processes and key intermediates for preparing atorvastatin.

Atorvastatin is preferably prepared as its calcium salt, i.e. [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[[phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2 : 1) 10 since the calcium salt is desirable and it enables easy formulation of atorvastatin for example, tablets, capsules, lozenges, powder and the like for oral administration.

One of the major drawbacks of the prior art processes referred to above is that none of these processes consistently produce amorphous 15 atorvastatin calcium but generally gives a mixture of its crystalline and amorphous forms, with unsuitable filtration and drying characteristics rendering them unsuitable for large-scale production.

PCT application, WO 97/03958 and WO 97/03959 disclose novel crystalline forms of atorvastatin calcium designated as Form I, Form II, 20 Form III and Form IV and method for their preparation which provide more favorable filtration and drying characteristics.

PCT application, WO 97/03960 and US Patent 6087511 describe the procedures for converting the crystalline form of atorvastatin calcium to the amorphous form. The process disclosed therein involve 25 dissolving form I atorvastatin calcium in a non hydroxylic solvent like tetrahydrofuran or a mixture of tetrahydrofuran and toluene. None of these processes disclosed therein is suitable for large scale production as solvent has to be removed at high temperature about 85 – 90°C and under high vacuum (5 – 10 mm of mercury) and the product thus 30 obtained is in the form of a brittle glassy foam which has to be broken into a free flowing powder. The process disclosed therein takes very long time for the removal of solvents

PCT application WO 00/71116 describes the procedure for converting the crystalline form-I by dissolving it in a non-hydroxylic

solvent like tetrahydrofuran and precipitating amorphous atorvastatin calcium by the addition of nonpolar hydrocarbon like, n-hexane cyclohexane or n-heptane. The method disclosed in this PCT application is not suitable for large scale production of amorphous atorvastatin calcium as the process requires very large amount of non polar hydrocarbon solvents making the process uneconomical on the commercial scale.

Objects of the invention

It is therefore, an object of the present invention to provide a process for the preparation of amorphous atorvastatin calcium which avoids all the disadvantages of the prior arts.

It is a further object of the present invention to provide a process for the preparation of amorphous atorvastatin calcium consistently and which avoids production of a mixture of amorphous and crystalline forms.

It is yet another object of the present invention to provide a process for the preparation of amorphous atorvastatin calcium, which is economical and capable of being practiced on a commercial scale.

It is a further object of the present invention to provide a process for the conversion of crystalline atorvastatin calcium in to its amorphous form, which is economical and is capable of being practiced on a commercial scale.

Summary of the invention

The above and other objects of the present invention are achieved by a novel process for the preparation of amorphous form of atorvastatin calcium directly from the intermediate (4R-cis)-1,1-dimethylethyl-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[[phenylamino]-carbonyl]-1H-pyrrol-1-yl]-ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate, diol protected tert-butyl ester (a) which is an intermediate in the synthesis of atorvastatin lactone, a starting material from which different polymorphs of atorvastatin calcium such as Form I and Form IV may be prepared. Similarly, preparation of Form II, Form III, and amorphous form by interconversion has been reported in the prior arts. However, to the applicants' knowledge, not a single process is

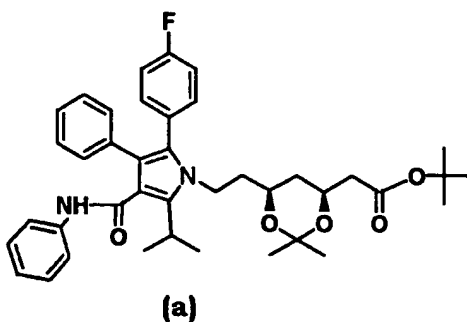
available to prepare amorphous form of atorvastatin calcium directly from the above mentioned intermediate (a), without employing corresponding lactone compound. Accordingly, the present invention discloses a novel process for the preparation of amorphous atorvastatin calcium from the above mentioned intermediate (a) on commercial scale, while in earlier prior arts, crystalline form - I of atorvastatin calcium is employed for the preparation of amorphous atorvastatin calcium. The present invention also discloses a novel process of converting form - I of atorvastatin calcium into amorphous form, which is suitable for converting all the crystalline forms of atorvastatin calcium in to amorphous form on commercial scale.

Detailed description

The process of the present invention eliminates the problems of prior arts. The present invention also discloses for the first time a process of manufacturing amorphous atorvastatin calcium directly from diol protected tert-butyl ester (a) as in scheme-1. The crude stage may contain some amount of calcium hydroxide, which is easily removed completely in the subsequent purification stage. At both the stages of preparation, atorvastatin calcium produced by the process of the present invention was found to be amorphous as revealed by X-ray powder diffraction data (figure -1, 2, 3 & 4). The present invention does not make use of any crystalline form to get amorphous atorvastatin calcium like other prior arts. However conversion of form- 1 of atorvastatin calcium in to amorphous atorvastatin calcium disclosed herein is an additional procedure within the scope of the present invention to exploit on commercial scale and does not in any way deviate from the basic purpose of this invention of getting amorphous atorvastatin calcium without employing any crystalline form. In the present invention, purification stage of atorvastatin calcium involves precipitation of pure amorphous atorvastatin calcium from aqueous ethyl acetate solution of the product by adding suitable nonpolar hydrocarbon solvent. European Patent Application 409281 mentions the use of ethyl acetate /hexane for

recrystallization without describing and claiming on the polymorphism of the product. The present invention does not employ corresponding lactone stage to convert into atorvastatin calcium like other prior arts.

Accordingly the present invention provides a process for the preparation of atorvastatin calcium in amorphous form which comprises
5 treating diol protected tert-butyl ester of the following structure (a)



10 with a methanolic solution in the presence of an aqueous acid, adding aqueous hydroxide solution to the reaction mixture and treating the product so obtained with calcium chloride solution to obtain crude atorvastatin calcium salt, isolating said crude salt and treating crude product so isolated with aqueous ethyl acetate and a non polar
15 hydrocarbon solvent to produce pure amorphous atorvastatin calcium. The pure product is then isolated by second filtration step followed by drying.

In a co-pending application No. 333/Mum/2001 of the applicants filed on April 11, 2001, the purification of the crude amorphous
20 atorvastatin calcium is achieved by isolating said crude salt and treating crude product so isolated with methanol and water to produce pure amorphous atorvastatin calcium. The pure product is then isolated by second filtration step followed by drying. The present invention on the other hand, dispenses with the treatment of crude amorphous
25 atorvastatin calcium with aqueous ethyl acetate and n-hexane for purification purpose .

Preferably, the aqueous acid is selected from hydrochloric acid , sulphuric acid, and formic acid; aqueous hydrochloric acid is being

most preferred. The aqueous hydroxide solution is selected from sodium hydroxide, potassium hydroxide, and lithium hydroxide; In a most preferred embodiment, aqueous sodium hydroxide is employed.

In another preferred embodiment, the crude salt as well as the
5 purified products are isolated by filtration and then dried.

In another preferred embodiment, the diol protected tert-butyl ester (a) is treated with 20 – 40 times w/v methanol. More preferably, the amount of methanol employed is 28 times w/v.

10 The HCl employed is preferably 2 – 6% aqueous w/v, more preferably 4% w/v in a molar ratio of 1.5 - 4, preferably 2.0. The reaction temperature is maintained at a range of from 20-40°C preferably, 30 -35°C for 8 - 20 hours preferably for 15 hours.

In another preferred embodiment, the dilute aqueous sodium
15 hydroxide solution employed ranges from 5 - 20% w/v, preferably 10% w/v in molar ratio of 1 - 1.5, more preferably, 1.35, (after calculating the amount of sodium hydroxide required for neutralization of hydrochloric acid present in the reaction mixture). The reaction mass is stirred for 2 - 6 hours, preferably, for 5 hours.

20 The pH of the reaction mixture is maintained 7.0 - 9.5, preferably 8.5 by addition of 4% w/v aqueous hydrochloric acid. In preferred embodiment, pH is always maintained at a level > 7.0.

The aqueous calcium chloride solution is employed in the range of 2 - 6% w/v preferably 4 – 5 % in the molar ratio of 1 – 2, preferably 1.65.
25 The reaction temperature is maintained at a temperature in the range of 50 - 55°C for 15 - 60 minutes preferably for 60 minutes.

The precipitated material is preferably cooled to 25 - 40°C, more preferably to 30 - 35°C, which is further cooled to 0 - 20°C preferably; to 10 - 15°C. The stirring is continued for 30 - 120 minutes preferably, for
30 60 minutes at 10 - 15°C The material is centrifuged easily and is preferably washed with D.M.Water to remove excess calcium chloride.

The present invention describes the method of converting diol protected tert-butyl ester (a) of atorvastatin directly into crude

amorphous atorvastatin calcium which contains some amount of calcium hydroxide which is removed in subsequent purification step.

The whole process consists of following key operations

In a most preferred embodiment of the present invention the entire
5 process will involve the following operations:

1) Treating of diol protected tert-butyl ester (a, scheme-1) in 20 - 40 times w/v methanol, as that of diol protected tert-butyl ester, preferably 28 times; with 2 -6% aqueous w/v hydrochloric acid preferably 4% w/v hydrochloric acid solution in a molar ratio of 1.5 -
10 4 preferably 2.0 at the temperature range of 20-40°C preferably at 30 -35°C for 8 - 20 hours preferably for 15 hours. HPLC analysis of reaction mixture after 15 hours shows the presence of unreacted diol protected tert-butyl ester - (a) (0.56%),. HPLC analysis also shows
15 formation of 4 intermediates (b,c,d,and e) as shown in scheme - 1 with distribution pattern as follows. This is an illustrative example, distribution pattern may vary depending on the reaction conditions.

(i)	atorvastatin diol tert-butyl ester (b)	-	72.00%
(ii)	atorvastatin diol methyl ester (c)	-	21.16%
(iii)	atorvastatin lactone (d)	-	2.52%
(iv)	atorvastatin diol acid (e)	-	0.96%

2) The above solution is treated with dilute aqueous sodium hydroxide solution ranging from 5 - 20% w/v preferably 10% w/v in molar ratio of 1 - 1.5 preferably 1.35 (after calculating the amount of sodium
25 hydroxide required for neutralization of hydrochloric acid present in the reaction mixture). The reaction mass is stirred for 2 - 6 hours preferably for 5 hours when HPLC analysis shows the complete conversion of all the intermediates (b,c,d and e) as mentioned in scheme -1 into a single product, atorvastatin sodium (f) in the
30 solution.

3) pH of the reaction mixture is adjusted between 7.0 - 9.5, preferably 8.5 by addition of 4% w/v aqueous hydrochloric acid, pH lower than 7.0 results in the formation of lactone compound (d) in the final

product, this also results in the decrease of the calcium content below the required amount i.e. 3.50 % w/w on dry basis.

- 4) The volume of the reaction mixture is then reduced to approximately 50% by distillation under reduced pressure below 60°C
- 5) The volume of the reaction mixture is measured and the content of methanol and water are determined v/v
- 6) The volume of the reaction mixture is then adjusted so that it contains 5 – 15 times, preferably 10 times methanol and 5 – 10 times, preferably 7 times water with respect to diol protected tert-butyl ester (a) initially taken.
- 7) The reaction mixture is then washed with 5 - 15 times preferably 10 times as that of diol protected tert-butyl ester (a) taken for reaction, with organic solvents insoluble in water such as toluene, xylene, diisopropyl ether, diethyl ether, dichloromethane preferably diisopropyl ether to remove starting material unreacted diol protected tert-butyl ester (a).
- 8) Aqueous methanolic layer after extraction with diisopropyl ether is charged into another S.S.Reactor, finally pH is checked and if necessary it is adjusted to 8.5, the reaction mixture is heated to 40 - 60°C preferably to 50 - 55°C.
- 9) Aqueous calcium chloride solution in the range of 2 - 6% w/v preferably 4 - 5 % in the molar ratio of 1 - 2 preferably 1.65 is added during 30 – 90 minutes preferably 60 minutes at 50 - 55°C with the smooth and uniform precipitation of atorvastatin calcium. If mode of addition is reversed, a sticky material is obtained under similar condition of operations.
- 10) The precipitated material is stirred at 50 - 55°C for 15 - 60 minutes preferably for 60 minutes.
- 11) The precipitated material is cooled to 25 - 40°C preferably to 30 - 35°C, which is further cooled to 0 - 20°C preferably to 10 - 15°C.
- 12) The stirring is continued for 30 - 120 minutes preferably for 60 minutes at 10 - 15°C.

- 13) The material is centrifuged easily and is washed with D.M. water to remove excess calcium chloride.
- 14) The wet cake of crude amorphous atorvastatin calcium which is 3 – 4 times as that of dried material, is dried in a vacuum dryer at 40 – 70°C preferably at 50 - 60°C for several hours preferably for 8 - 10 hours till the water content in the range of 2 – 8% preferably 4 – 6% is achieved.
- 15) The dried material was found to contain traces of calcium hydroxide which is formed during the calcium chloride addition (excess sodium hydroxide in the reaction mixture reacts with calcium chloride to produce calcium hydroxide) which is insoluble in water and hence can not be removed even washing with plenty of D.M. Water. The next operations afterwards are being carried out to remove calcium hydroxide present in the crude amorphous atorvastatin calcium.
- 16) X-Ray powder diffraction study shows crude atorvastatin calcium to be amorphous. Till this stage, the process of the present invention is identical to the process of the co-pending application No. 333/Mum/2001 dated April 11, 2001.

20

The present invention is characterized by the following purification steps:

- 17) Crude amorphous atorvastatin calcium containing traces of calcium hydroxide is dissolved in ethyl acetate in volume 5 – 15 times as that of crude amorphous atorvastatin calcium preferably 8 times in volume containing 2 - 7% preferably 3.5 - 4% water at 40 - 70°C preferably at 50 - 60°C.
- 18) The solution is then treated with activated carbon for 30 minutes and filtered to get absolutely clear transparent solution of atorvastatin calcium in an aqueous ethyl acetate, devoid of calcium hydroxide. The material is precipitated by adding non-polar hydrocarbon solvent which is soluble in ethyl acetate such as n-hexane, n-heptane, cyclohexane etc. at a temperature 15 - 40°C

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preferably at 25 - 35°C. The addition of non-polar hydrocarbon solvent results in the precipitation of the material which is cooled to 0 - 20°C, preferably to 10 - 15°C for 15 - 90 minutes preferably for 60 minutes. The material is recovered by filtration and dried at 20 - 70°C
5 preferably 50 - 60°C for 5 - 20 hours preferably for 8 - 10 hours.

- 19) The volume of filtered aqueous ethyl acetate solution of atorvastatin calcium is adjusted to 7 - 15 times, more preferably 10 times in volume as that of crude amorphous atorvastatin calcium by
10 adding filtered ethyl acetate.
- 20) The water content in aqueous ethyl acetate solution of atorvastatin calcium after make up with fresh ethyl acetate is adjusted 2 - 7%, more preferably 3.5 - 4.0% v/v before the addition of non polar hydrocarbon solvent to precipitate pure material.
- 15 21) The amount of non polar hydrocarbon solvent to precipitate the material from aqueous ethyl acetate solution of atorvastatin calcium is 0.5 - 5 times, more preferably 1 - 2 times in volume as that of aqueous ethyl acetate solution of atorvastatin calcium.
- 22) X-Ray powder diffraction study shows pure atorvastatin calcium to
20 be amorphous.
(Fig 2,3 and 4) and the material was found to be free from calcium hydroxide.

**Major advantages of the present invention compared to the prior art
25 processes are:-**

1. Direct conversion of diol protected tert-butyl ester (a, scheme-1) into amorphous atorvastatin calcium without preparation and isolation of lactone compound.
2. Unreacted diol protected tert-butyl ester (a) and calcium hydroxide
30 formed are being removed during the process.
3. Crystalline forms of atorvastatin calcium are conveniently converted into amorphous atorvastatin calcium using purification procedures disclosed herein.
4. The process disclosed herein does not require vigorous stirring.

5. Avoiding the need to remove the solvent at higher temperature and under high vacuum.
6. Avoiding the need of using an uneconomical solvent like tetrahydrofuran.
- 5 7. The process disclosed herein gives amorphous form directly without interconversion of any crystalline form into amorphous form.
8. Residual solvent levels in the final product is well below the allowable limits i.e. n-hexane 2000 - 2250 ppm, ethyl acetate 200 - 250 ppm.

10

The present invention will now be described in greater detail with reference to the accompanying drawings and examples in which Figure 1 depicts X-ray Powder diffractogram of crude amorphous atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

15

Figures 2, 3 & 4 shows X-ray powder diffractograms of purified amorphous atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

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Figure 5 shows X-ray powder diffractogram of form - I of atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

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Figure 6 teaches X-ray powder diffractogram of amorphous atorvastatin calcium prepared by converting form - I of atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

30

Scheme 1 describes schematic representation and distribution of the intermediates formed during the treatment of methanolic solution of diol protected tert-butyl ester (a)

with dilute hydrochloric acid and subsequent conversion of all the intermediates (b,c,d & e) as in scheme-I into a single product atorvastatin sodium (f) and then to atorvastatin calcium.

5 The present invention will now be illustrated by the following examples, which are not intended to limit the effective scope of the claims. Consequently, any variations of the invention described above are not to be regarded as departure from the spirit and scope of the invention as claimed. The present invention has been described in terms
10 of its specific embodiments and certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of present invention.

EXAMPLES

15

Example 1

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H pyrrole-1-heptanoic acid hemicalcium salt (Crude amorphous atorvastatin calcium).

20

20 Kg. of diol protected tert-butyl ester (a) is suspended in 560 lt. methanol in GLR and treated with 55 lt. of 4% aqueous w/v hydrochloric acid for 15 hours at 30 - 35°C then a solution of 4 Kg. sodium hydroxide in 40 lt. D.M.Water is added in 1 hour and stirring is continued for 5
25 hours. The pH of reaction mixture is adjusted to 8.5 by addition of 1 lt. of 4% w/v aqueous hydrochloric acid. The volume of the reaction mixture is reduced to approximately 50% by distilling below 60°C under vacuum (distilled volume 270 - 275 lt.). the analysis of the contents left behind in the reactor shows water content to be 83 lt. and methanol
30 content to be 178 lt. Then 23 lt. methanol and 57 lt. water are added to the reaction mixture, reaction mixture is washed with 200 lt. of diisopropylether. Aqueous methanolic solution containing atorvastatin sodium is charged into another S.S.Reactor and finally pH is checked and if necessary adjusted to 8.5 and the contents are heated to 50 -

55°C to which a aqueous solution of 2.8 Kg. calcium chloride in 60 lt. water is added in 1 hour at 50 - 55°C with the precipitation of atorvastatin calcium, the precipitated mass is stirred for 1 hr at 50 - 55°C which is cooled to 30 - 35°C (within 60 minutes), then cooled to 10 - 15°C (within 60 minutes), the precipitated material is further stirred for 1 hr at 10 - 15°C. The solid material is centrifuged and washed with D.M.Water. (Wet weight = 55 - 60 Kg.) The material is dried at 50 - 60°C for 8 hours till water content 4 - 6% is achieved giving 17.50 Kg. crude amorphous atorvastatin calcium. X-ray powder diffraction data confirmed the amorphous nature of the product.(Fig-1).

Example 2

The examples disclosed herein are purification stages in which calcium hydroxide present in atorvastatin calcium is being removed.

Method A :-

25 g crude amorphous atorvastatin calcium obtained in example 1 is stirred with 200 ml ethyl acetate containing 9.0 ml D.M.Water at 50-55°C. The resulting hazy solution is stirred with 1.0 g activated carbon at 50 - 55°C for 15 min. The solution is then cooled to 30 - 35°C and filtered through hyflow bed, with 2 x 25 ml ethyl acetate wash. The combined filtrate is passed through 5 micron filter to get a clear solution. The total volume of the filtrate is adjusted to 250 ml by adding fresh ethyl acetate. The water content of filtrate is adjusted to 3.5 - 4% v/v, if necessary. To this solution 250 ml filtered n-hexane is added slowly at 30 - 35°C and stirred for 20 minutes, upon addition of n-hexane pure amorphous atorvastatin calcium is precipitated. The precipitated material is then stirred for 1 hour at 10 - 15°C. The product is filtered and washed with 2 x 20 ml n-hexane and dried at 50 - 60°C for 10 hours till the moisture content in the product 4 - 6% w/w is achieved. The dried weight thus obtained is 24.1 gm. X-Ray powder diffraction data confirms the amorphous nature of the product. (Fig. - 2)

Method B :

100 g crude amorphous atorvastatin calcium obtained in example 1 is stirred with 800 ml ethyl acetate containing 30 ml D.M. Water at 50-55°C atorvastatin calcium is dissolved in aqueous ethyl acetate solution
5 resulting in a hazy solution to which 5 g activated carbon is added and the reaction mixture is stirred for 50 - 55°C for 30 minutes. The mixture is cooled to 30 - 35°C then it is filtered through hyflow bed with 2 x 200 ml ethyl acetate wash. The combined filtrate is then passed through 5 micron filter. The volume of the filtrate is then adjusted to 1 lt. by adding
10 filtered fresh ethyl acetate. The water content in ethyl acetate solution of atorvastatin calcium is adjusted to 3.5 - 4.0 % v/v if necessary.

(i) To 500 ml of the above ethyl acetate solution, 750 ml filtered n-hexane is slowly added in 20 minutes with stirring at 30 - 35°C. The precipitation starts during the addition of n-hexane. It is then cooled
15 to 10 - 15°C with stirring and the temperature is maintained for 60 min. The solid is collected by filtration and washed with 2 x 50 ml n-hexane. The product is dried at 50 - 55°C for 8 - 10 hrs. till the water content between 4 - 6% w/w is achieved, the dried weight thus obtained is 46 gm and X-Ray powder diffraction data confirms
20 the nature of material to be amorphous (Fig. - 3).

(ii) To remaining 500 ml ethyl acetate of atorvastatin calcium (obtained in method B), 1 liter filtered n-hexane was added with stirring at 30-35°C in 20 - 25 minutes. Similar procedures were followed as in (i) of method B. The weight of product after drying is 44 gm. X-Ray
25 powder diffraction data reveals the nature of the product to be amorphous. (Fig. - 4)

Example 3

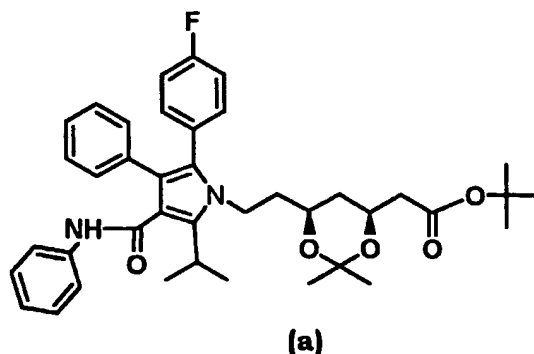
The example disclosed herein is a convenient procedure to convert crystalline forms of atorvastatin calcium in to amorphous atorvastatin calcium, exemplified here by converting form - I of atorvastatin calcium in to amorphous form.
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25 g atorvastatin calcium form - I is stirred with 200 ml ethyl acetate containing 9.0 ml D.M. Water at 50- 55°C. The resulting hazy

solution is stirred with 1.0 g activated carbon at 50 - 55°C for 15 min. The solution is then cooled to 30 - 35°C and filtered through hyflow bed, with 2 x 25 ml ethyl acetate wash. The combined filtrate is passed through 5 micron filter to get a clear solution. The total volume of the
5 filtrate is adjusted to 250 ml by adding fresh ethyl acetate. The water content of filtrate is adjusted to 3.5 - 4% v/v, if necessary. To this solution 250 ml filtered n-hexane is added slowly at 30 - 35°C and stirred for 20 minutes, upon addition of n-hexane, pure amorphous atorvastatin calcium is precipitated. The precipitated material is then
10 stirred for 1 hour at 10 - 15°C. The product is filtered and washed with 2 x 20 ml n-hexane and dried at 50 - 60°C for 10 hours till the water content in the product 4 - 6% w/w is achieved. The dried weight thus obtained is 24.1 gm. X-Ray powder diffraction data confirms the amorphous nature of the product. (Fig. - 6)

WE CLAIM :-

1. A process for the preparation of atorvastatin calcium in amorphous form which comprises (i) treating diol protected tert-butyl ester of the following structure (a)



- 5 with a methanolic solution in the presence of an aqueous acid;
- (ii) adding aqueous hydroxide solution to the reaction mixture; and removing unreacted diol protected tert-butyl ester (a) by solvent extraction (iii) treating the product obtained in step (ii) with calcium
- 10 chloride solution to obtain crude amorphous atorvastatin calcium salt;
- (iv) isolating said crude salt; (v) treating crude product so isolated with activated carbon in aqueous ethyl acetate (vi) recovering the product by addition of non polar hydrocarbon solvent filtration and drying to produce pure amorphous atorvastatin calcium.
- 15 2. A process as claimed in claim 1 wherein said aqueous acid is selected from hydrochloric acid, sulfuric acid and formic acid.
3. A process as claimed in claim 2 wherein said aqueous acid is aqueous hydrochloric acid.
4. A process as claimed in claim any one of claims 1 to 3 wherein
- 20 said aqueous hydroxide solution is selected from sodium hydroxide, potassium hydroxide and lithium hydroxide
5. A process as claimed in claim 4 wherein said aqueous hydroxide employed is dilute aqueous sodium hydroxide.
- 25 6. A process as claimed claim 1 wherein the said crude salt as well as the purified products are isolated by filtration and then dried.

7. A process as claimed in claim 1 wherein said diol protected tert-butyl ester (a) is treated with 20 – 40 times w/v methanol as that of compound (a) taken for reaction.
- 5 8. A process as claimed in claim 7 wherein said amount of methanol is 28 times w/v methanol as that of compound (a) taken for reaction.
9. A process as claimed in any preceding claim wherein said hydrochloric acid employed is 2 – 6% aqueous w/v.
- 10 10. A process as claimed in claim 9 wherein said hydrochloric acid is 4% w/v.
11. A process as claimed in claim 9 or 10 wherein said hydrochloric acid is employed in a molar ratio of from 1.5 - 4.
12. A process as claimed in claim 11 wherein said molar ratio is 2.0.
- 15 13. A process as claimed in claim 1 wherein the reaction temperature is maintained at range of from 20-40°C.
14. A process as claimed in claim 13 wherein said reaction temperature is 30 -35°C.
15. A process as claimed in claim 1 wherein said reaction is carried
20 out for 8 - 20 hours.
16. A process as claimed in claim 15 wherein said reaction time is 15 hours.
17. A process as claimed in claim 1 wherein four products (b,c,d, and
25 e) as shown in scheme -1 are formed in a mixture in varying proportions on the treatment of methanolic solution of protected diol tert-butyl ester (a) with a dilute hydrochloric acid and intermediates (b,c,d, and e) thus formed are converted into a single product atorvastatin sodium (f) in solution with the subsequent treatment of sodium hydroxide.
- 30 18. A process as claimed in claim any one of claims 5 to 16 wherein said dilute aqueous sodium hydroxide solution employed ranges from 5 - 20% w/v.
19. A process as claimed in claim 18 wherein said dilute sodium hydroxide solution employed is a molar ratio of 1 - 1.5

20. A process as claimed in claim 19 wherein said molar ratio is 1.35, (after calculating the amount of sodium hydroxide required for neutralization of hydrochloric acid present in the reaction mixture).
- 5 21. A process as claimed in claim 1 wherein in step (ii) the reaction mass is stirred for 2 - 6 hours.
22. A process as claimed in claim 21 wherein said reaction mass is stirred for 5 hours.
- 10 23. A process as claimed in any preceding claim wherein unreacted diol protected tert-butyl ester (a) present in the reaction mixture is removed by solvent extraction.
24. A process as claimed in claim 23 wherein the solvent employed is selected from toluene, xylene, diisopropyl ether, diethyl ether and dichloromethane.
- 15 25. A process as claimed in claim 23 and 24 wherein the solvent employed is diisopropyl ether to remove unreacted diol protected tert-butyl ester (a) from the reaction mixture.
26. A process as claimed in claim 1 wherein the pH of the reaction mixture is maintained in the range of 7.0 - 9.5.
- 20 27. A process as claimed in claim 26 wherein said pH is 8.5.
28. A process as claimed in claim 27 wherein said pH of 8.5 is achieved by the addition of 4% w/v aqueous hydrochloric acid.
29. A process as claimed in claim 1 wherein said aqueous calcium chloride solution employed is in the range of 2 - 6% w/v.
- 25 30. A process as claimed in claim 29 wherein said aqueous calcium chloride solution employed is in the range of 4 - 5 %.
31. A process as claimed in claim 29 and 30 wherein said aqueous calcium chloride solution employed is in a molar ratio of 1 - 2.
- 30 32. A process as claimed in claim 31 wherein said molar ratio is 1.65.
33. A process as claimed in claim 1 wherein after the addition of aqueous calcium chloride, the reaction temperature is maintained in the range of 50 - 55°C for 15 - 60 minutes.

31. A process as claimed in claim 1 wherein the percentage of water in ethyl acetate solution of atorvastatin calcium is 2 – 7 % v/v before crystallizing out amorphous atorvastatin calcium by addition of non-polar hydrocarbon solvent.
- 5 32. A process as claimed in claim 31 wherein the percentage of water in ethyl acetate solution of atorvastatin calcium is 3.5 – 4.0 % v/v before crystallizing out amorphous atorvastatin calcium by addition of non-polar hydrocarbon solvent.
- 10 33. A process as claimed in claim 1 wherein the amount of activated carbon is 2 – 10 % as that of crude amorphous atorvastatin calcium.
34. A process as claimed in claim 33 wherein the amount of activated carbon is 4 – 5 % as that of crude amorphous atorvastatin calcium.
- 15 35. A process as claimed in claim 33 and 34 wherein said treatment with activated carbon is carried out at 50 - 55°C.
36. A process as claimed in any one of claims 33 to 35 wherein the said treatment with activated carbon is carried out for about 10 to 60 minutes.
- 20 37. A process as claimed in any one of claims 33 to 36 wherein the said treatment with activated carbon is carried out for about 15 to 30 minutes.
- 25 38. A process as claimed in claim 1 wherein the non-polar hydrocarbon solvents like n-hexane, n-heptane, and cyclohexane are employed to precipitate the pure amorphous atorvastatin calcium.
39. A process as claimed in claim 38 wherein the non-polar hydrocarbon solvent is n-hexane.
- 30 40. A process as claimed in claim 38 and 39 wherein the amount of n-hexane employed for the precipitation of pure amorphous

atorvastatin calcium is 1 to 5 times v/v as that of ethyl acetate solution of atorvastatin calcium.

41. A process as claimed in claim 40 wherein the amount of n-hexane employed for the precipitation of pure amorphous atorvastatin calcium is 1 to 2 times v/v as that of ethyl acetate solution of atorvastatin calcium.
42. A process as claimed in claim 1 wherein the percentage of methanol in aqueous methanolic solution of atorvastatin sodium before the addition of aqueous solution of calcium chloride is 30 - 80% v/v.
43. A process as claimed in claim 42 wherein the percentage of methanol in aqueous methanolic solution of atorvastatin sodium before the addition of aqueous solution of calcium chloride is 60% v/v.
44. A process as claimed in claim 1 wherein the preparation of atorvastatin calcium in amorphous form is achieved substantially as described herein with reference to the accompanying examples and drawings.
45. A process as claimed in any preceding claim wherein crystalline forms of atorvastatin calcium are converted in to amorphous atorvastatin calcium.
46. A process as claimed in claim 1 wherein the amount of ethyl acetate employed for the dissolution of crude amorphous atorvastatin calcium is 5 to 10 times as that of crude amorphous atorvastatin calcium.
47. A process as claimed in claim 46 wherein the amount of ethyl acetate employed for the dissolution of crude amorphous atorvastatin calcium is 7 times as that of crude amorphous atorvastatin calcium.
48. A process as claimed in claim 1 wherein the volume of ethyl acetate solution of crude amorphous atorvastatin calcium is 5 - 15 times, as that of amorphous atorvastatin calcium before addition of non-polar hydrocarbon solvent to precipitate pure amorphous atorvastatin calcium.

49. A process as claimed in claim 48 wherein the volume of ethyl acetate solution of crude amorphous atorvastatin calcium is 10 times, as that of amorphous atorvastatin calcium before addition of non-polar hydrocarbon solvent to precipitate pure amorphous atorvastatin calcium.
50. A process as claimed in claim 1 wherein the amount of methanol employed is 5 – 15 times as that of protected diol tert-butyl ester (a) before the addition of aqueous calcium chloride solution.
51. A process as claimed in claim 50 wherein the amount of methanol employed is 10 times as that of protected diol tert-butyl ester (a) before the addition of aqueous calcium chloride solution.
52. A process as claimed in claim 1 wherein the amount of water employed is 5 – 10 times as that of protected diol tert-butyl ester (a) before the addition of aqueous calcium chloride solution.
53. A process as claimed in claim 52 wherein the amount of water employed is 7 times as that of protected diol tert-butyl ester (a) before the addition of aqueous calcium chloride solution.
54. A process as claimed in claim 1 wherein calcium hydroxide present in crude amorphous atorvastatin calcium is removed in purification stage.
55. A process as claimed in claim 1 wherein protected diol tert-butyl ester (a) is employed to prepare amorphous atorvastatin calcium.
56. A process as claimed in claim 1 wherein corresponding lactone compound is not employed for the preparation of amorphous atorvastatin calcium.
57. A process as claimed in claim 1 wherein crystalline forms of atorvastatin calcium are not employed for the preparation of amorphous atorvastatin calcium in basic scope of the present invention disclosed herein.
58. A process as claimed in claim 1 wherein crystalline forms of atorvastatin calcium are converted into amorphous atorvastatin calcium as an additional procedure, included in basic scope of the present invention disclosed herein.

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

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- (2 - 7 above are inventors and applicants for USA only)

Hereby appoints (appoint) the following persons as:

☒ agent☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

SUBRAMANIAM, Hariharan; NATARAJ, Guruswamy; PRITHVIRAJ, Susheela, VENKITESHWARA, Prithviraj

SUBRAMANIAM, NATARAJ & ASSOCIATES,

Attorneys at Law Patent & Trademark Attorneys: E 556, Greater Kailash II, New Delhi - 110 048, INDIA

To represent the undersigned before

☒

all the competent Authorities

☐

the International Searching Authority only

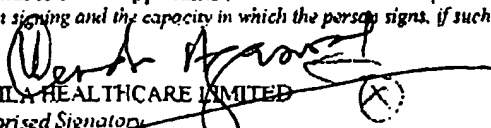
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the International Preliminary Examining Authority only

In connection with the international application identified below:

Title of the invention: **PROCESS FOR THE PRODUCTION OF ATORVASTATIN CALCIUM IN AMORPHOUS FORM**Applicant's or agents file reference: **HSM/334/MUM**International application number (if already available): **PCT/IN01/00111**filed with the following Office **RO/IN MUMBAI** as receiving Office
and to make or receive payments on behalf of the undersigned

Signatures of the applicants (where there are several persons, each of them must sign; next to the each signature, indicate the name and of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):



CADILA HEALTHCARE LIMITED
Authorized Signatory

Date: **July 13, 2001**

SCHEME: 1

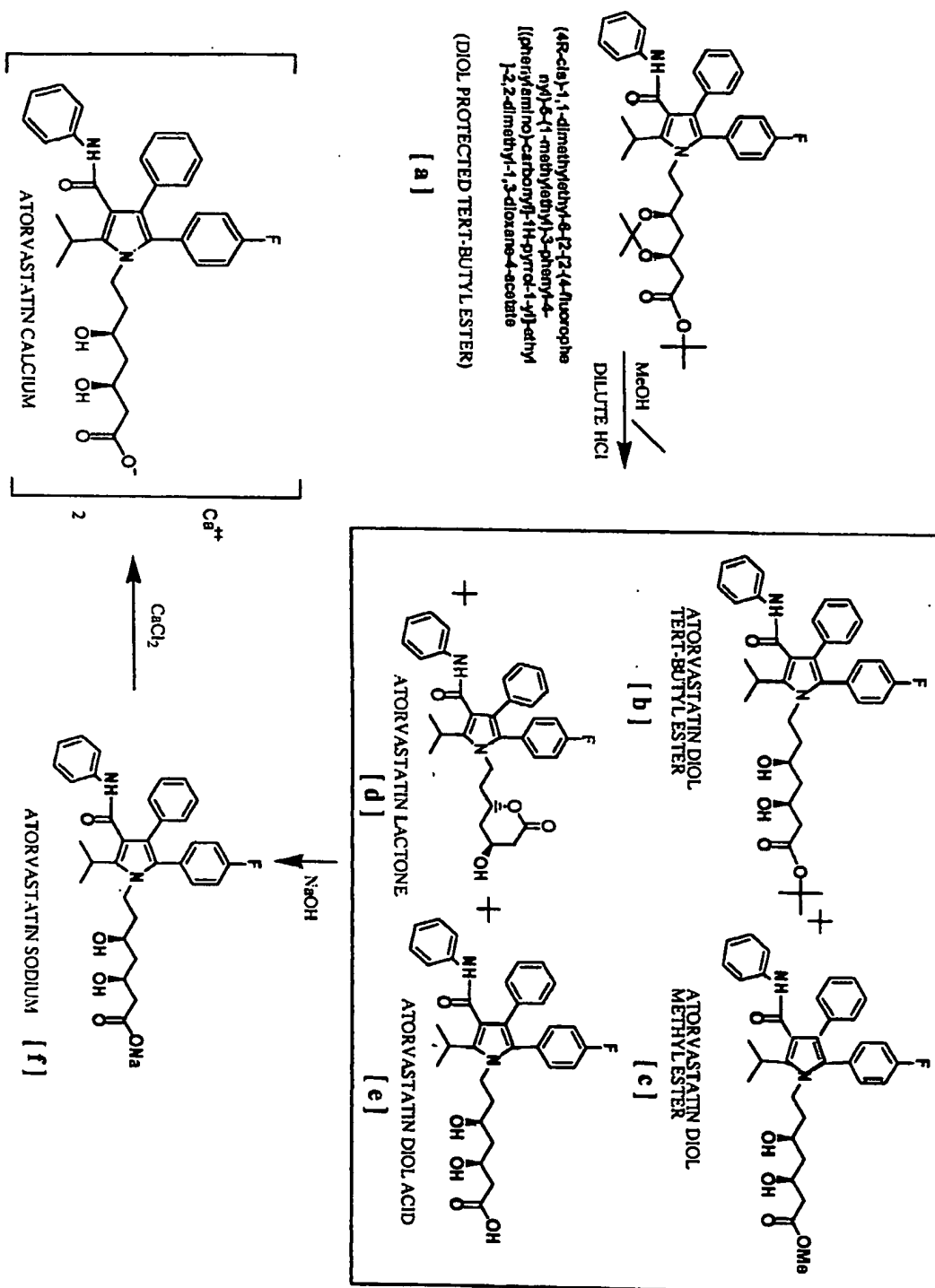


Figure - 1**Smoothing**

Sample name: AT-Ca-OAC18025CRUDE File : OAC18025.raw Date : January-17-01 16:02:56 Operator : Administrator
Comment : AT-Ca-OAC18025 CRUD Memo :
Method : Averaging Smoothing Points: 99

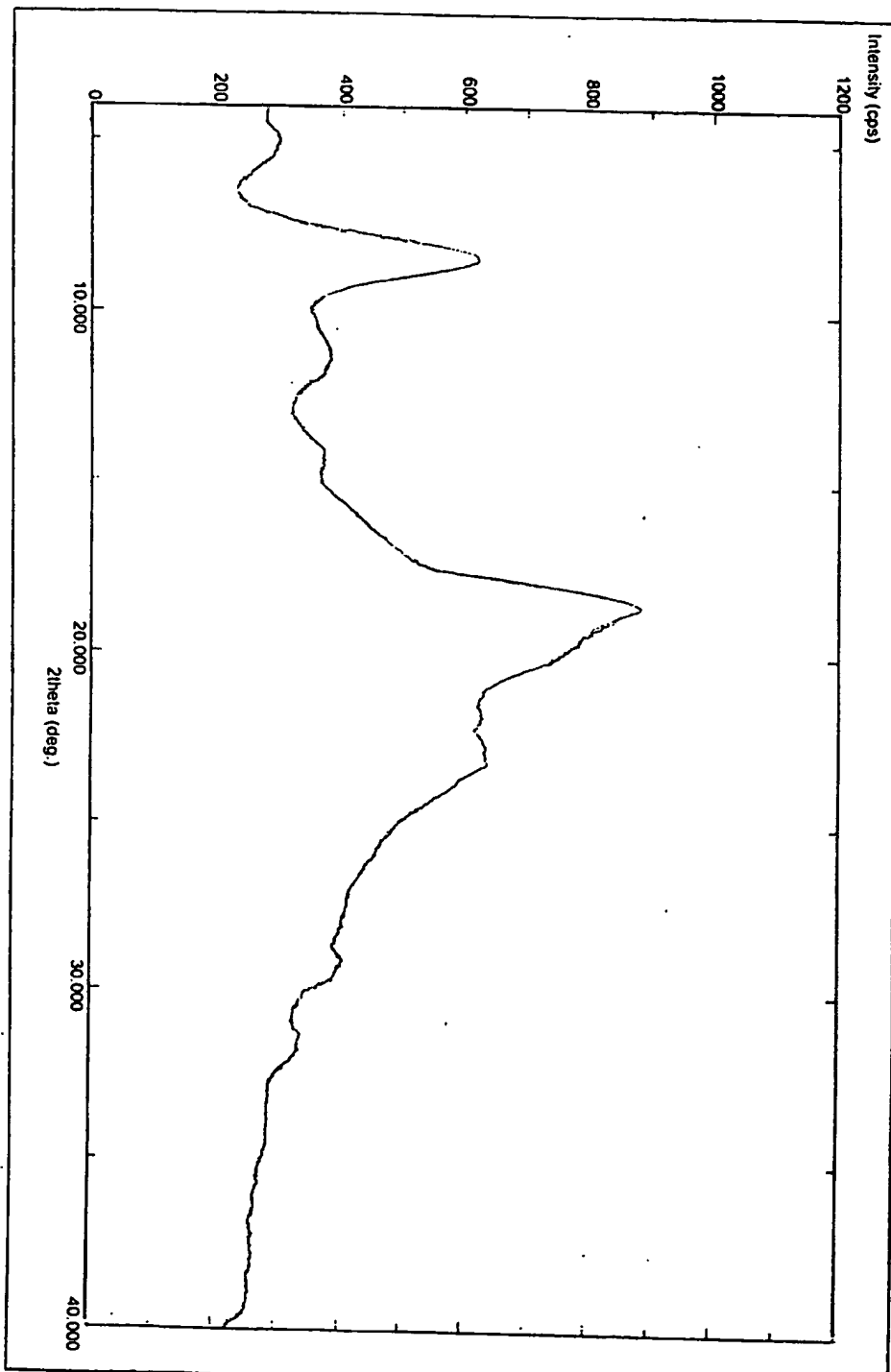
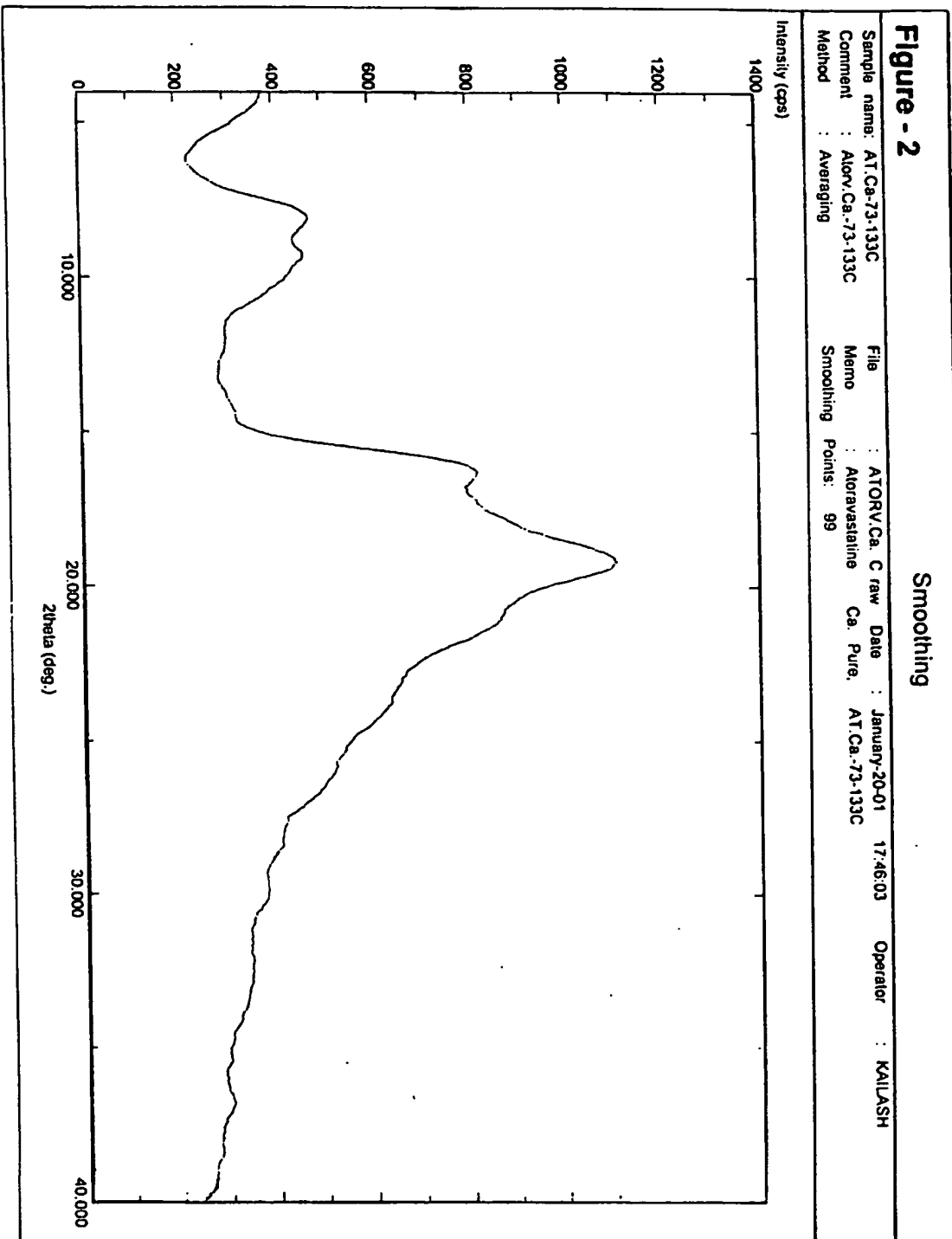
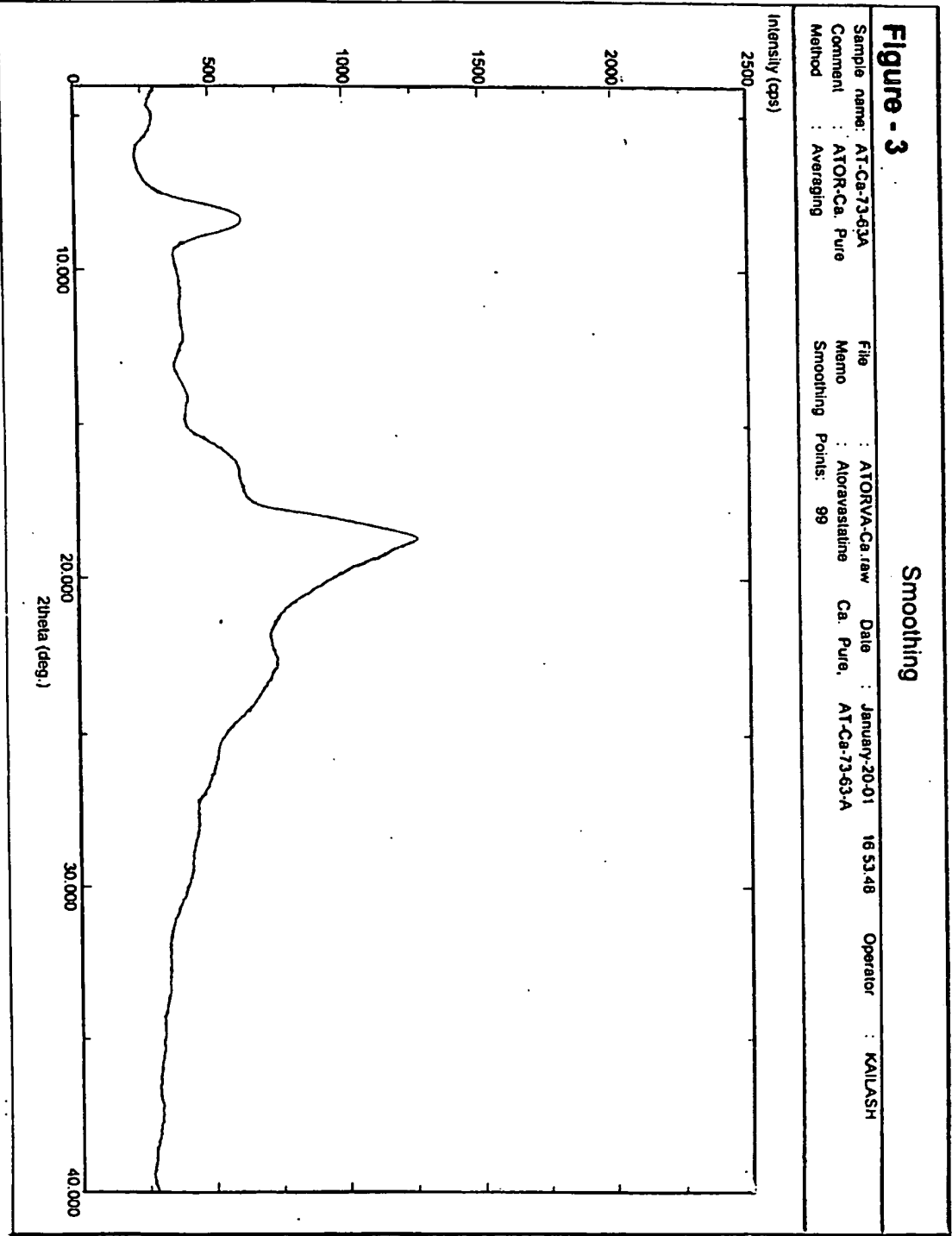
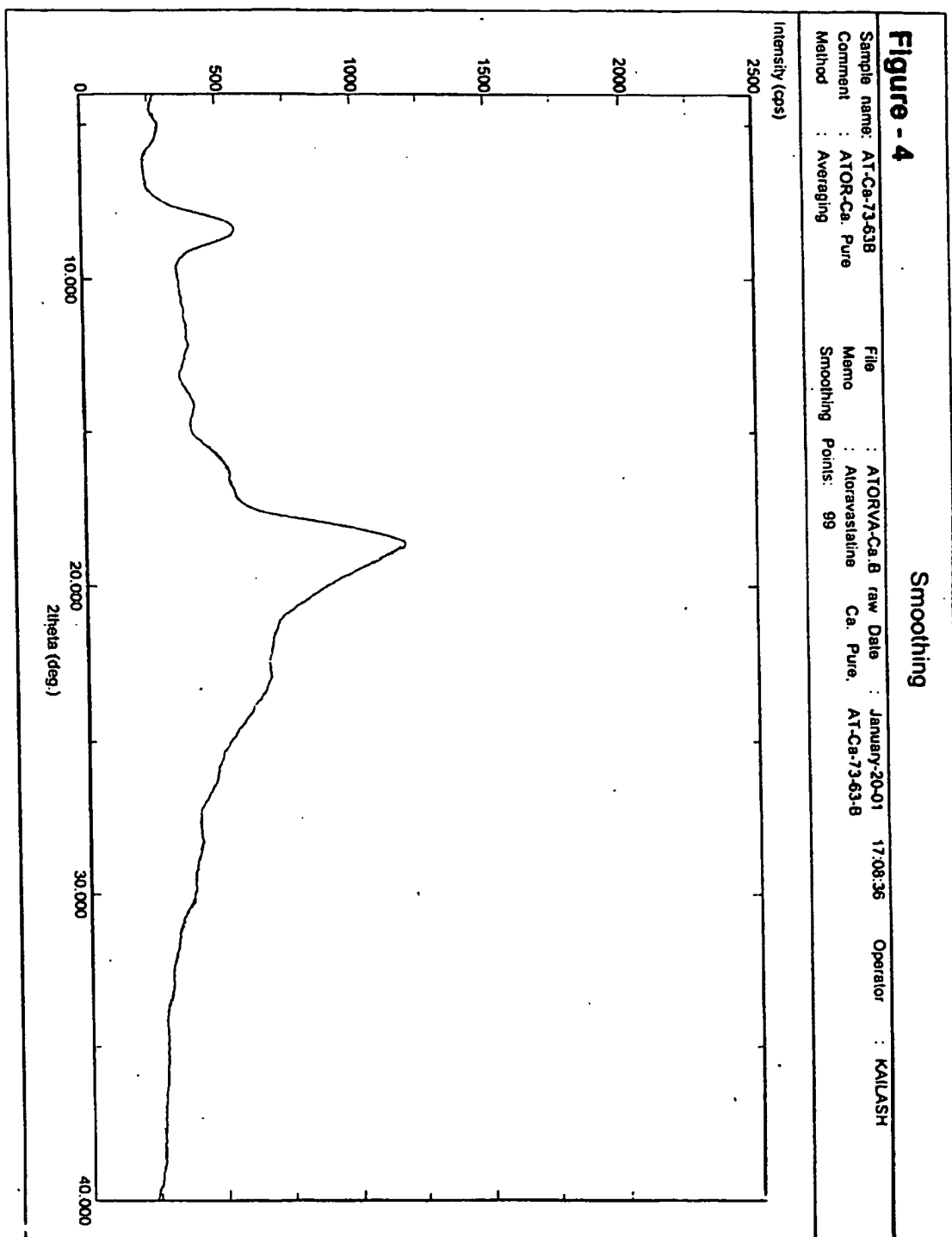


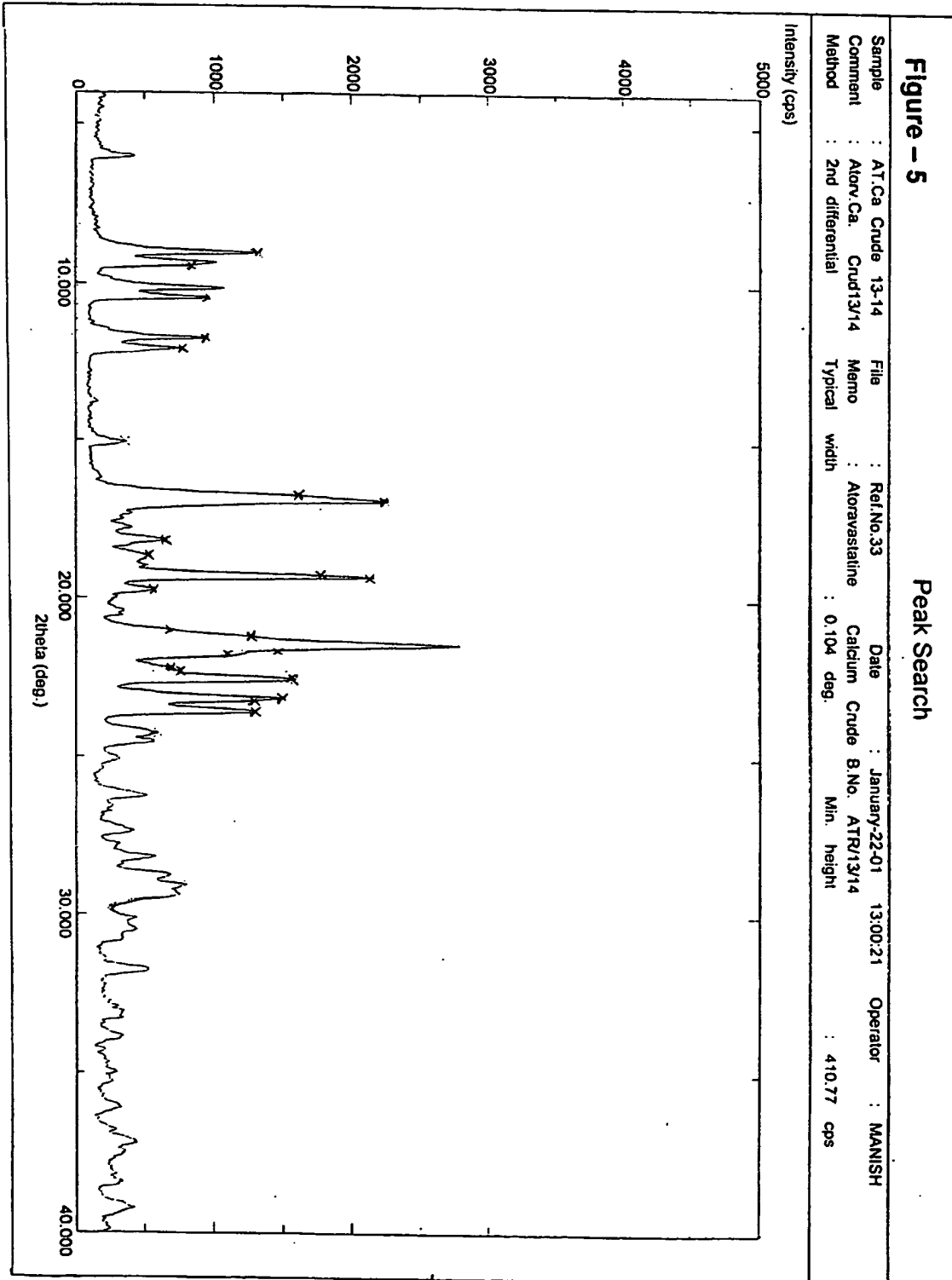
Figure - 2

Smoothing





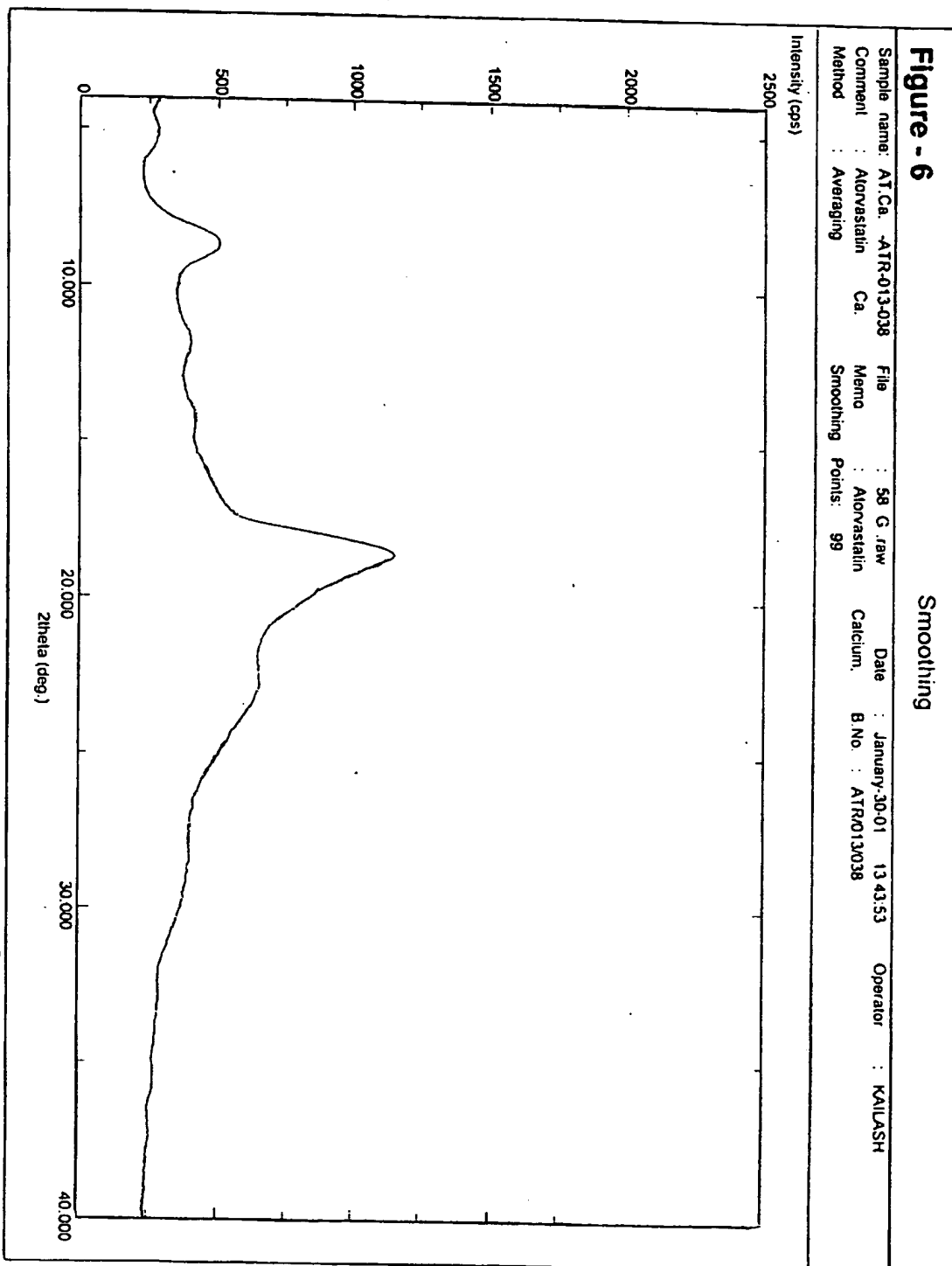




Peak Search

Peak Search

Sample	AT Ca Crude 13-14	File	Ref.No.33	Date	January-22-01	13:00:21	Operator	MANISH			
Comment	Alorv.Ca. Crud13/14	Memo	Alorvastatine	Calcium	Crude B No.	ATR13/14					
Method	2nd differential	Typical	width	0.104 deg.	Min. height						
Peak no.	2theta	FWHM	d-value	Intensity	I/Io	Peak no.	2theta	FWHM	d-value	Intensity	I/Io
1	9.020	0.129	9.7959	1323	48	31	28.770	0.082	3.1005	672	25
2	9.320	0.106	9.4812	1027	37	32	29.020	0.153	3.0744	812	30
3	9.420	0.094	9.3808	844	31	33	29.240	0.059	3.0517	729	27
4	10.140	0.141	8.7163	1083	39	34	29.340	0.059	3.0416	759	28
5	10.450	0.141	8.4584	976	35	35	29.430	0.106	3.0325	676	25
6	11.710	0.106	7.5509	860	35	36	30.090	2.9674	439	16
7	12.050	0.106	7.3386	782	28	37	30.440	2.9341	435	16
8	15.030	5.8896	361	13	38	30.760	2.9043	341	13
9	16.750	0.153	5.2885	1617	58	39	31.700	2.8203	518	19
10	16.930	0.176	5.2327	2251	81	40	33.290	2.6891	327	12
11	18.180	0.176	4.8756	669	24	41	33.820	2.6482	340	13
12	18.650	0.082	4.7538	543	20	42	34.960	2.5644	285	11
13	19.260	0.059	4.6046	1785	64	43	36.040	2.4900	308	11
14	19.330	0.141	4.5881	2137	77	44	37.110	2.4206	432	16
15	19.730	0.200	4.4960	575	21	45	38.390	2.3428	326	12
16	20.990	0.071	4.2288	688	25	46	39.190	2.2968	385	14
17	21.210	0.094	4.1855	1280	46						
18	21.460	0.176	4.1373	2797	100						
19	21.530	0.082	4.1240	2325	84						
20	21.830	0.176	4.0680	1132	41						
21	22.200	0.094	4.0010	690	25						
22	22.330	0.071	3.8780	767	28						
23	22.570	0.271	3.9362	1588	57						
24	23.150	0.106	3.8389	1501	54						
25	23.240	0.071	3.8243	1302	47						
26	23.590	0.224	3.7683	1308	47						
27	24.250	0.071	3.6672	606	22						
28	24.500	0.176	3.6304	566	21						
29	28.130	0.129	3.1696	586	21						
30	28.670	0.141	3.1111	670	24						



INTERNATIONAL SEARCH REPORT

Inte - Application No
PC., ... 01/00111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 the whole document --- -/--	1-6,17

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

5 April 2002

Date of mailing of the international search report

15/04/2002

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INTERNATIONAL SEARCH REPORT

 Interr Application No
 PC1, ... 01/00111

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRAUL A ET AL: "ATORVASTATIN CALCIUM" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 22, no. 9, 1997, pages 956-968, XP000904817 ISSN: 0377-8282 scheme 1, compound (XIX) scheme 2, compounds (XXIV), (XIX) scheme 4, compound (XLIII) ---	1-6,17
X	WO 94 16693 A (WARNER LAMBERT CO) 4 August 1994 (1994-08-04) example A ---	1-6,17
X	US 5 273 995 A (ROTH BRUCE D) 28 December 1993 (1993-12-28) cited in the application scheme 2 example 10 ---	1-6,17
X	WO 97 03960 A (WARNER LAMBERT CO ;LIN MIN (US); SCHWEISS DIETER (US)) 6 February 1997 (1997-02-06) cited in the application claim 1 ---	45,58
X	WO 00 71116 A (THAPER RAJESH KUMAR ;KUMAR YATENDRA (IN); RANBAXY LAB LTD (IN); KU) 30 November 2000 (2000-11-30) claim 1 ---	45,58
E	WO 01 42209 A (LEK TOVARNA FARMACEVTSKIH ;PFLAUM ZLATKO (SI)) 14 June 2001 (2001-06-14) claim 1 -----	45,58

INTERNATIONAL SEARCH REPORT

nation on patent family members

Intern Application No

PCT, ... 01/00111

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9416693	A	04-08-1994	AT 178794 T	15-04-1999
			CA 2150372 A1	04-08-1994
			DE 69324504 D1	20-05-1999
			DE 69324504 T2	26-08-1999
			DK 680320 T3	25-10-1999
			EP 0680320 A1	08-11-1995
			ES 2133158 T3	01-09-1999
			GR 3030359 T3	30-09-1999
			JP 8505640 T	18-06-1996
			MX 9400281 A1	29-07-1994
			SG 45369 A1	16-10-1998
			WO 9416693 A1	04-08-1994
			US 5686104 A	11-11-1997
			US 6126971 A	03-10-2000
US 5273995	A	28-12-1993	MX 9203143 A1	01-07-1992
			AT 207896 T	15-11-2001
			AU 628198 B2	10-09-1992
			AU 5972490 A	24-01-1991
			CA 2021546 A1	22-01-1991
			DE 1061073 T1	03-05-2001
			DE 69033840 D1	06-12-2001
			DK 409281 T3	25-02-2002
			EP 1061073 A1	20-12-2000
			EP 0409281 A1	23-01-1991
			ES 2153332 T1	01-03-2001
			FI 94339 B	15-05-1995
			IE 902659 A1	27-02-1991
			JP 3058967 A	14-03-1991
			KR 167101 B1	15-01-1999
			NO 174709 B	14-03-1994
			NO 176096 B	24-10-1994
			NZ 234576 A	23-12-1992
			PT 94778 A ,B	20-03-1991
			SG 46495 A1	20-02-1998
			ZA 9005742 A	25-03-1992
WO 9703960	A	06-02-1997	AT 199542 T	15-03-2001
			AU 700794 B2	14-01-1999
			AU 6497896 A	18-02-1997
			BG 102188 A	31-08-1998
			BR 9609714 A	23-02-1999
			CA 2220455 A1	06-02-1997
			CN 1190956 A	19-08-1998
			CZ 9800122 A3	16-12-1998
			DE 69611999 D1	12-04-2001
			DE 69611999 T2	26-07-2001
			DK 839132 T3	09-04-2001
			EE 9700369 A	15-06-1998
			EP 0839132 A1	06-05-1998
			ES 2156997 T3	01-08-2001
			HR 960312 A1	28-02-1998
			HU 220343 B	28-12-2001
			IL 122161 A	14-07-1999
			JP 11510486 T	14-09-1999
			NO 980209 A	16-01-1998
			PL 324463 A1	25-05-1998
			PT 839132 T	29-06-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 01/00111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703960 A		SI 839132 T1	30-06-2001
		SK 5898 A3	05-08-1998
		WO 9703960 A1	06-02-1997
		US 6274740 B1	14-08-2001
WO 0071116 A	30-11-2000	AU 1996700 A	12-12-2000
		EP 1185264 A1	13-03-2002
		WO 0071116 A1	30-11-2000
WO 0142209 A	14-06-2001	SI 20425 A	30-06-2001
		AU 1543801 A	18-06-2001
		WO 0142209 A1	14-06-2001